doi:10.1038/nature10865

**Supplementary Table 1.** Data collection and structure refinement statistics.

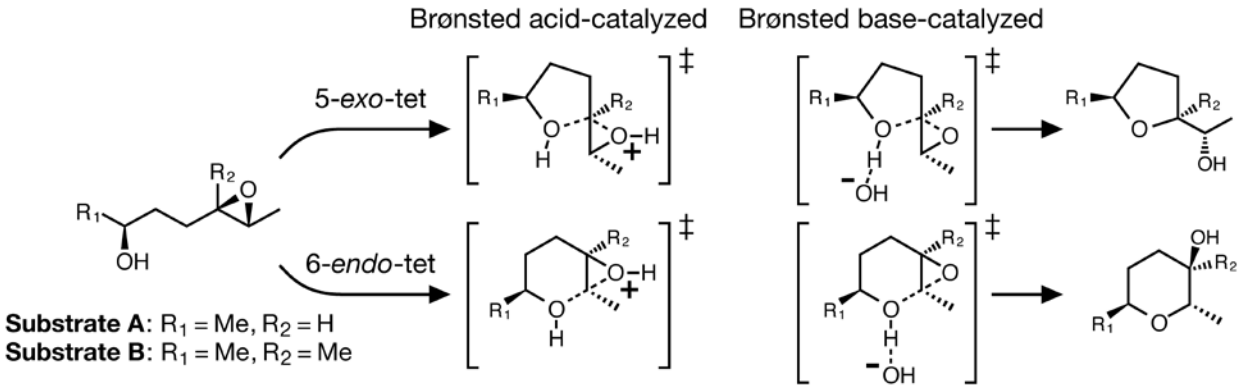
| | | |
|---|---|---|
| **Data Collection** | | |
| Space group | | *C*2 |
| Unit cell dimensions | a, b, c (Å) | 117.9, 47.5, 62.3 |
| | β (°) | 120.1 |
| Molecules/asymmetric unit | | 1 |
| Resolution range (Å) | | 29.4–1.59 (1.63–1.59) |
| $R_{sym}$ [a] (%) | | 9.4 (94.1) |
| I/σ (I) | | 12.2 (1.7) |
| Total no. of reflections | | 183,191 |
| No. of unique reflections | | 39,256 |
| Redundancy | | 4.7 (4.7) |
| Completeness (%) | | 97.2 (96.0) |
| **Refinement Statistics** | | |
| Resolution limit (Å) | | 29.45–1.59 |
| No. of reflections | | 37,288 |
| $R_{work}$ [b]/$R_{free}$ (%) | | 17.3 / 19.3 (29.2 / 32.3) |
| Estimated coordinate error (Å) | | 0.056 |
| **Number of atoms** | | |
| Protein | | 2,126 |
| Ligands | | 60 |
| Buffers / Ion | | 34 |
| Water | | 163 |
| **B-factors (Å$^2$)** | | |
| Protein | | 19.7 |
| Ligands | | 23.3 |
| Buffers / Ion | | 33.0 |
| Water | | 29.5 |
| **Root mean square deviations** | | |
| Bond lengths (Å) | | 0.015 |
| Bond angles (°) | | 1.781 |

Values in parentheses are for the highest resolution shell.

[a] $R_{sym} = \sum | I_{avg} - I_i | / \sum I_i$, where $I_i$ is the observed intensity and $I_{avg}$ is the average intensity of observations of symmetry-related reflections.

[b] $R_{work} = \sum | F_p - F_{p(calc.)} | / \sum F_p$, where $F_p$ and $F_{p(calc.)}$ are observed and calculated structure factors; $R_{free}$ is calculated with 5% of the data.

**Supplementary Table 2.** Benchmarking of the B2PLYP and M06-2X calculations with different zeta-valence polarized basis sets on the acid- and base-catalyzed, 5-*exo*-tet and 6-*endo*-tet cyclizations of the model substrates **A** and **B**. To calculate the energy difference between 5-*exo* and 6-*endo* epoxide openings, we have carried out quantum mechanical calculations to locate the transition structures for both processes. Under acidic conditions this reaction is catalyzed by protonation of the epoxide, while under basic conditions the nucleophilic alcohol may be activated by a general base. We considered these two catalytic scenarios individually, investigating the cyclization of two model systems: a disubstituted (substrate **A**) and a trisubstituted (substrate **B**) epoxide as shown in the scheme given below. Both types of substrates are implicated in the biosynthesis of polyethers (as can be seen in Fig. 1b), while substrate **B** represents a good model for bisepoxyprelasalocid A **2** (Fig. 1c) in terms of the substitution pattern of the epoxide and the stereochemistry.




**Substrate A**, Brønsted acid-catalyzed:

| | 5-*exo*-tet | 6-*endo*-tet | $\Delta\Delta G^{\ddagger}$ |
|---|---|---|---|
| B2PLYP/*triple*-ζ | –1.6 | –1.3 | 0.3 |
| B2PLYP/*double*-ζ | –2.2 | –2.0 | 0.2 |
| M06-2X/*triple*-ζ | –2.1 | 0.2 | 2.3 |
| M06-2X/*double*-ζ | –2.5 | –0.3 | 2.2 |

**Substrate B**, Brønsted acid-catalyzed:

| | 5-*exo*-tet | 6-*endo*-tet | $\Delta\Delta G^{\ddagger}$ |
|---|---|---|---|
| B2PLYP/*triple*-ζ | 13.9 | 18.7 | 4.8 |
| B2PLYP/*double*-ζ | 14.6 | 18.9 | 4.3 |
| M06-2X/*triple*-ζ | 16.5 | 22.2 | 5.7 |
| M06-2X/*double*-ζ | 17.9 | 22.7 | 4.8 |

**Substrate A**, Brønsted base-catalyzed:

| | 5-*exo*-tet | 6-*endo*-tet | $\Delta\Delta G^{\ddagger}$ |
|---|---|---|---|
| B2PLYP/*triple*-ζ | 7.7 | 11.8 | 4.1 |
| B2PLYP/*double*-ζ | 7.0 | 11.3 | 4.3 |
| M06-2X/*triple*-ζ | 14.3 | 17.4 | 3.1 |
| M06-2X/*double*-ζ | 13.3 | 16.5 | 3.2 |

**Substrate B**, Brønsted base-catalyzed:

| | 5-*exo*-tet | 6-*endo*-tet | $\Delta\Delta G^{\ddagger}$ |
|---|---|---|---|
| B2PLYP/*triple*-ζ | 11.0 | 13.0 | 2.0 |
| B2PLYP/*double*-ζ | 11.7 | 14.7 | 3.0 |
| M06-2X/*triple*-ζ | 18.9 | 19.8 | 0.9 |
| M06-2X/*double*-ζ | 19.2 | 20.9 | 1.7 |

Explanation of methods examined: B2PLYP/*triple*-ζ = B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d); B2PLYP/*double*-ζ = B2PLYP/6-31G(d); M06-2X/*triple*-ζ = M06-2X/6-311++G(d,p)//M06-2X/6-31G(d); M06-2X/*double*-ζ = M06-2X/6-31G(d). ZPE (unscaled), enthalpic and entropic contributions computed at the same level as geometry optimization.

**Supplementary Table 3.** Comparison of the effect of solvation on the B2PLYP and M06-2X calculations performed on the model systems examined in this study. Free energy barriers were obtained for 5-*exo*-tet and 6-*endo*-tet cyclizations following optimizations of the competing transition structures (TSs). The optimized cyclization TSs for substrates **A** and **B** are shown in Supplementary Table 2. Since epoxide opening is irreversible under both acidic and basic conditions, a comparison of the activation barriers allows a prediction of the product ratio. Although alternative TSs leading to a flipped 5- or 6-membered ring product were also obtained, we only considered the lowest energy, and hence the most important TS. For the disubstituted epoxide **A**, the computed activation barriers show that the 5-*exo*-tet cyclization (i.e., expected according to Baldwin's rules) is favored over the competing 6-*endo*-tet cyclization under both acidic and basic catalysis. For acid catalysis the preference for 5-membered ring formation is 0.4 kcal/mol, while for base catalysis the preference is increased to 4.3 kcal/mol. Under both sets of conditions, 5-membered ring formation is preferred. Both electrophilic termini of the epoxide share similar electronic and steric characteristics, but orbital overlap with the incipient nucleophile is maximized in the 5-*exo* TS. For substrate **B**, a closer representative of **2** (Fig. 1c), the steric and electronic environments at each end of the epoxide are uneven. Computed barriers show that 5-*exo*-tet cyclization is favored under acidic conditions to a larger extent (4.1 kcal/mol), because more highly substituted carbon is better able to stabilize the positive charge. In contrast, under basic catalysis the preference for the 5-membered ring is now reduced (1.2 kcal/mol) due to the increased steric hindrance of nucleophilic attack at the more substituted epoxide terminus. Our quantum chemical calculations show a lower energetic barrier for the 5-membered ring formation, which is in agreement with general experimental observations and also with Baldwin's rules. However, the calculations also indicate that the preference for the 5-membered ring formation is smaller for the base-catalyzed pathway for substrate **B**.

**Substrate A**, Brønsted acid-catalyzed:

| | 5-*exo*-tet | 6-*endo*-tet | $\Delta\Delta G^{\ddagger}$ |
|---|---|---|---|
| B2PLYP/*water* | 2.3 | 2.7 | 0.4 |
| B2PLYP/*DCM* | 1.8 | 2.2 | 0.4 |
| M06-2X/*water* | 1.8 | 4.3 | 2.5 |
| M06-2X/*DCM* | 1.3 | 3.8 | 2.5 |

**Substrate B**, Brønsted acid-catalyzed:

| | 5-*exo*-tet | 6-*endo*-tet | $\Delta\Delta G^{\ddagger}$ |
|---|---|---|---|
| B2PLYP/*water* | 16.9 | 21.0 | 4.1 |
| B2PLYP/*DCM* | 16.5 | 20.7 | 4.2 |
| M06-2X/*water* | 19.4 | 24.5 | 5.1 |
| M06-2X/*DCM* | 19.0 | 24.2 | 5.2 |

**Substrate A**, Brønsted base-catalyzed:

| | 5-*exo*-tet | 6-*endo*-tet | $\Delta\Delta G^{\ddagger}$ |
|---|---|---|---|
| B2PLYP/*water* | 13.5 | 17.8 | 4.3 |
| B2PLYP/*DCM* | 12.8 | 17.1 | 4.3 |
| M06-2X/*water* | 19.8 | 22.6 | 2.8 |
| M06-2X/*DCM* | 19.1 | 21.9 | 2.8 |

**Substrate B**, Brønsted base-catalyzed:

| | 5-*exo*-tet | 6-*endo*-tet | $\Delta\Delta G^{\ddagger}$ |
|---|---|---|---|
| B2PLYP/*water* | 11.8 | 13.0 | 1.2 |
| B2PLYP/*DCM* | 11.7 | 13.0 | 1.3 |
| M06-2X/*water* | 18.3 | 18.4 | 0.1 |
| M06-2X/*DCM* | 18.1 | 18.3 | 0.2 |

Explanation of methods examined: B2PLYP = B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d); M06-2X = M06-2X/6-311++G(d,p)//M06-2X/6-31G(d). Single-point solvation corrections use a CPCM model with UFF radii and are performed on the gas-phase geometries at the same level of theory.

**Supplementary Table 4.** Comparison of the theozyme calculations with B2PLYP vs. M06-2X functionals and different zeta-valence polarized basis sets on the 5-*exo*-tet and 6-*endo*-tet cyclizations.

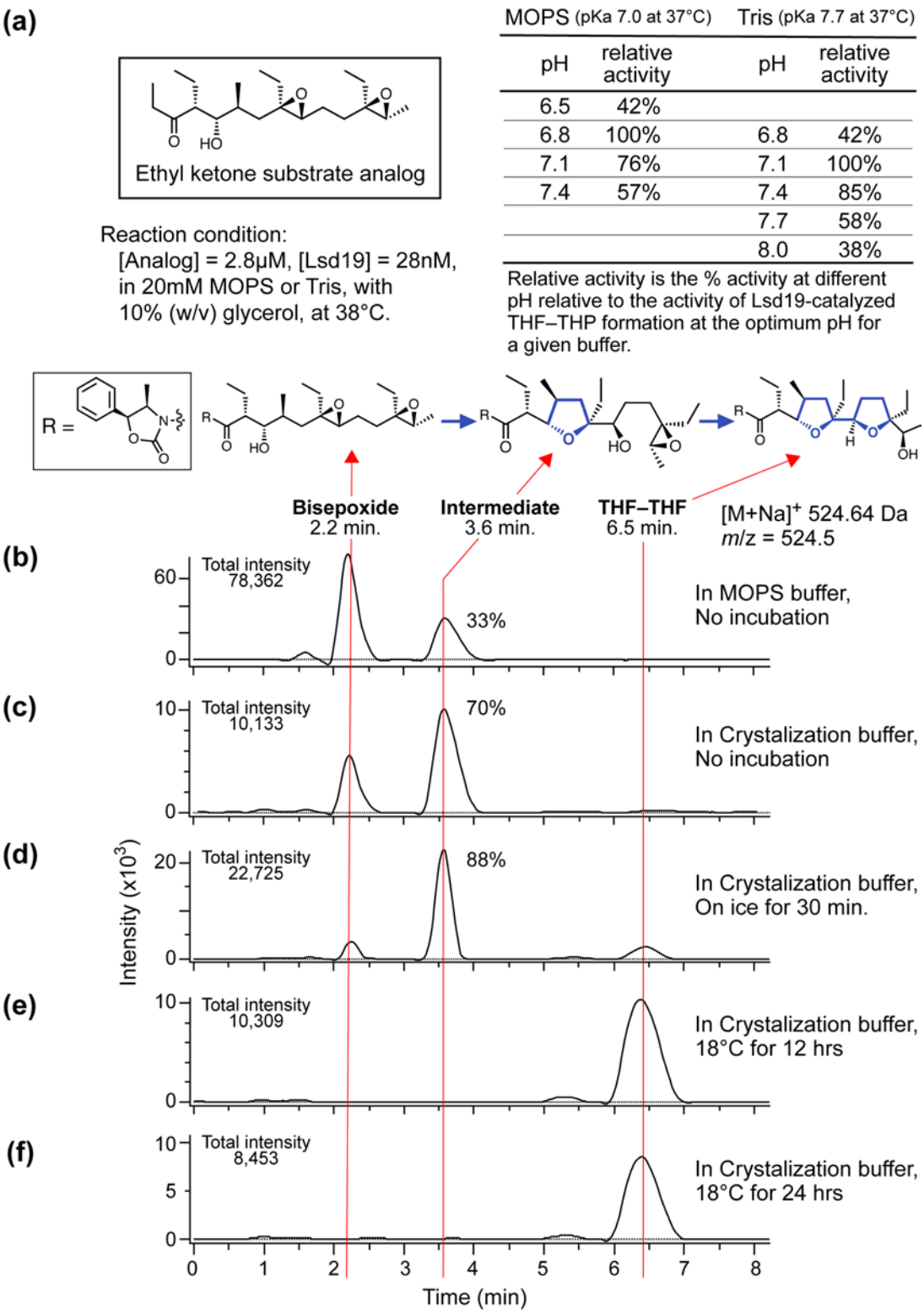
**Theozyme calculation**, activation barrier:

| | 5-*exo*-tet | 6-*endo*-tet | $\Delta\Delta E^{\ddagger}$ |
|---|---|---|---|
| M06-2X/*double*-ζ | 28.8 | 25.9 | –2.9 |
| M06-2X/*triple*-ζ | 27.8 | 24.6 | –3.2 |
| B2PLYP/*triple*-ζ | 20.5 | 18.0 | –2.5 |
| MP2/*triple*-ζ | 25.5 | 21.4 | –4.1 |
| M06-2X/*ether* | 28.8 | 25.8 | –3.0 |

**Theozyme calculation**, $\Delta E_{rxn}$:

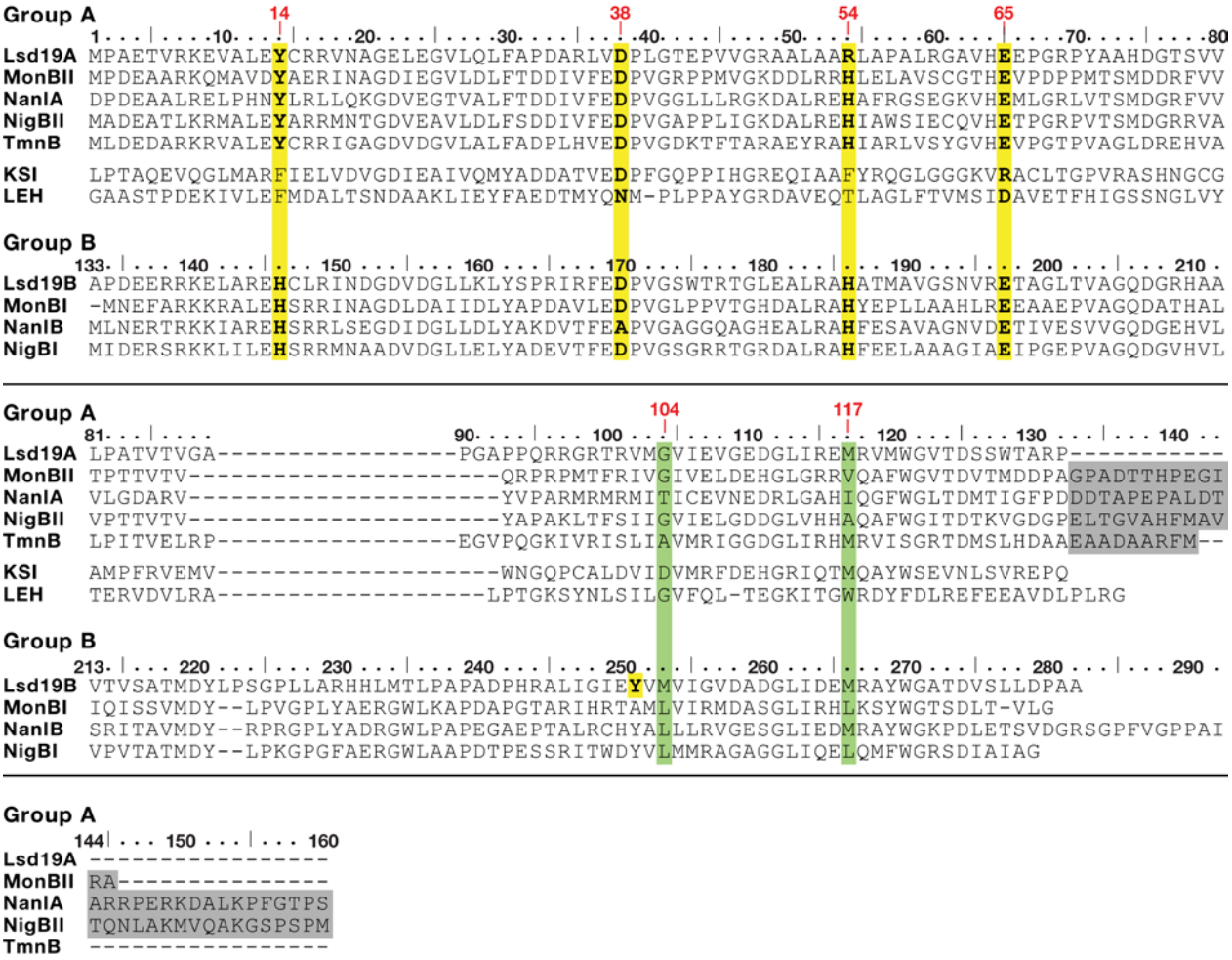
| | 5-*exo*-tet | 6-*endo*-tet | $\Delta\Delta E^{\ddagger}$ |
|---|---|---|---|
| M06-2X/*double*-ζ | –1.5 | –7.4 | –5.9 |
| M06-2X/*triple*-ζ | 0.5 | –6.0 | –5.5 |
| B2PLYP/*triple*-ζ | –2.0 | –6.6 | –4.6 |
| MP2/*triple*-ζ | –1.9 | –7.5 | –5.6 |
| M06-2X/*ether* | –2.5 | –7.9 | –5.4 |

Explanation of methods examined: Optimization at the M06-2X/6-31G(d) level; *double*- and *triple*-ζ refer to 6-31G(d) and 6-311++G(d,p) basis sets, respectively. Single-point solvation correction for diethylether (ether; ρ=4.24) uses a CPCM model with UFF radii performed on the gas-phase geometry.

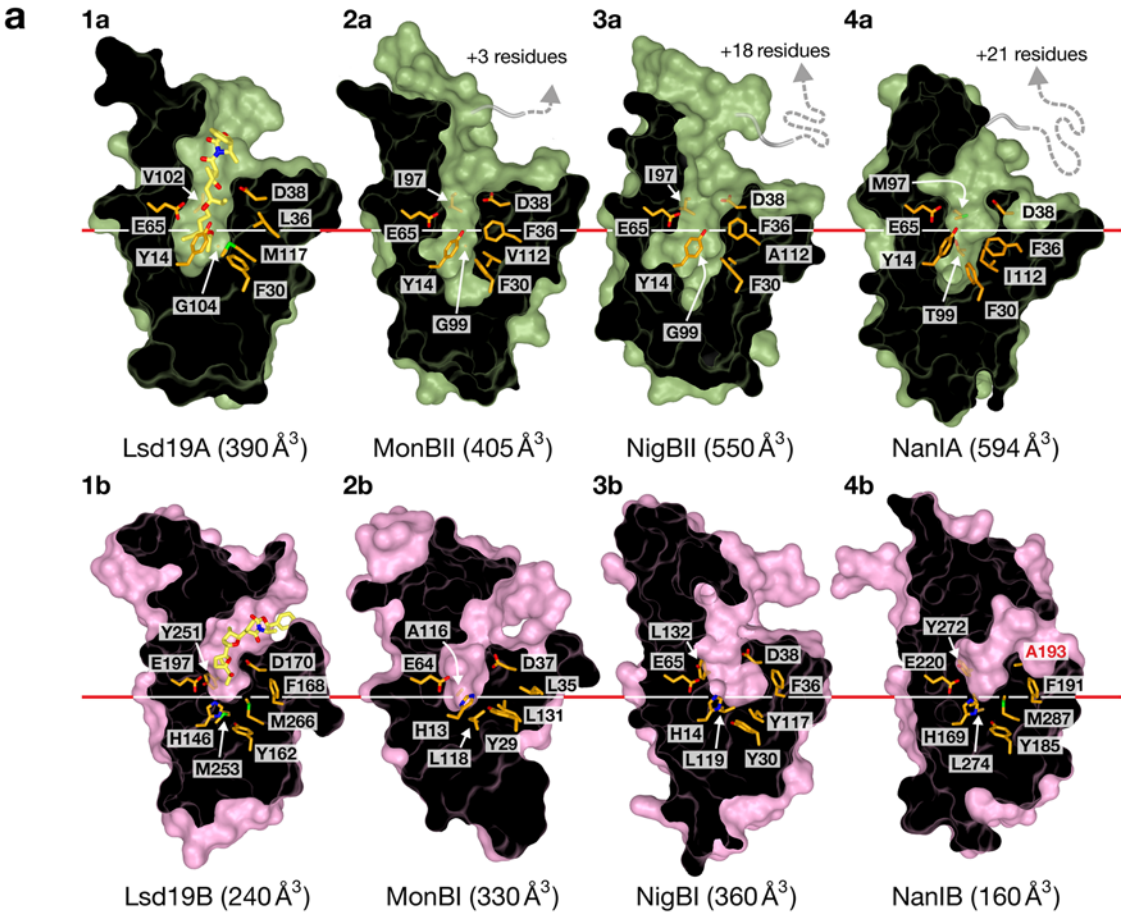


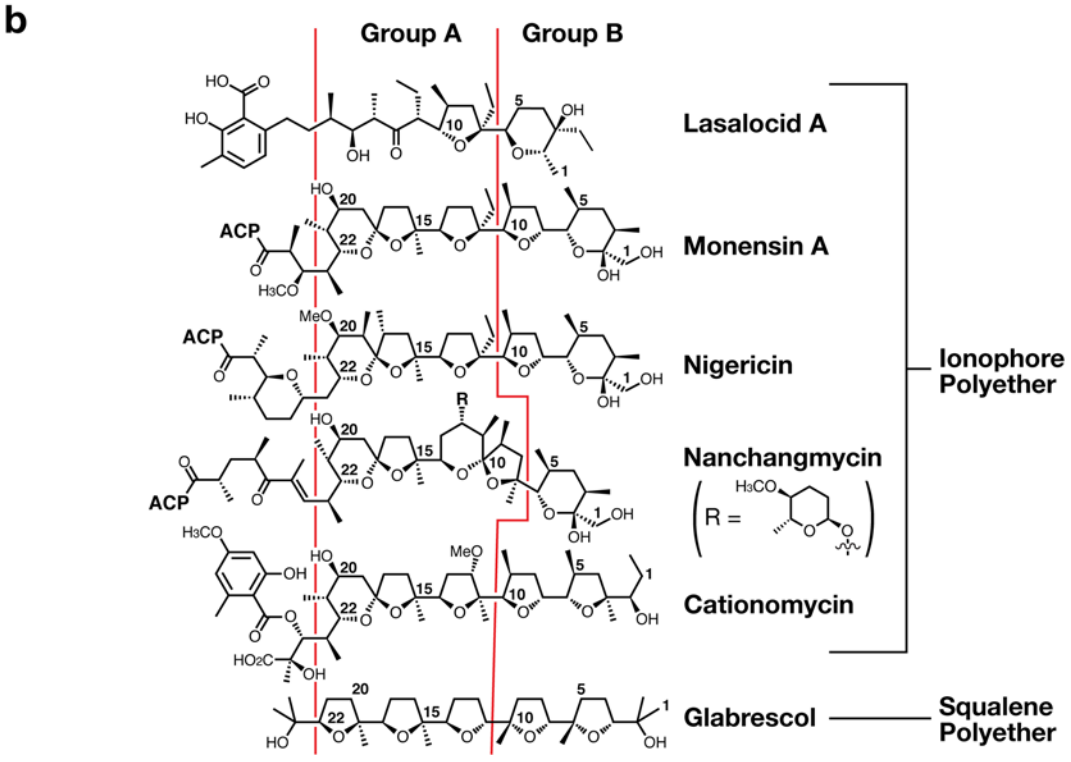

**Supplementary Figure 1.** Characterization of cyclization of bisepoxide substrate analogs. **(a)** pH-dependence of Lsd19-catalyzed formation of THF–THP product from the ethyl ketone

bisepoxide substrate analog. The optimum activity is observed at around pH 7 with a quick loss of activity as the pH is shifted lower. **(b–f)** Spontaneous cyclization of the bisepoxide substrate analog used for crystallization. Cyclization was followed under the condition used for Lsd19 crystallization. Stock methanol solution of the substrate was mixed with MOPS buffer (20mM MOPS pH 6.8) or with the crystallization buffer (100mM sodium acetate pH 4.6, 1.6M sodium formate and 17.1mM 1,5-diaminopentane with the protein buffer comprised of 50mM potassium phosphate pH 7.0, 1mM EDTA and 15mM β-mercaptoethanol) to the final concentration of 0.2μM. The mixture was immediately injected into LC–MS for analysis (**panels b** and **c**). The crystallization buffer mixture was incubated on ice for 30 min, and an aliquot was analyzed by LC–MS (**panel d**). The mixture was incubated at 18°C for additional 12 and 24 hours, and aliquot was taken at each time point and analyzed by LC–MS (**panels e** and **f**). In both the MOPS and crystallization buffers, a significant level of monocyclized intermediate was observed immediately after the substrate was mixed with the buffer (**panels b** and **c**). In the crystallization buffer, a gradual increase of the intermediate was observed when the mixture was kept on ice (**panel c** vs. **d**). Finally, a complete conversion of the substrate into the THF–THF product was observed by 12 hours of incubation in the crystallization buffer at 18°C (**panels e** and **f**). **Panel b** shows that 33% of the substrate was in the form of intermediate when the sample was analyzed immediately after mixing the substrate with the MOPS buffer (20mM MOPS pH 6.8). Our experience indicates that the majority of the intermediate is likely formed while the sample is being analyzed by LC–MS. Similarly, **panel c** shows that 70% of the substrate existed as the intermediate when the sample was analyzed immediately after mixing the substrate with the crystallization buffer. The level of intermediate is significantly higher than in (**b**), presumably because of the lower pH in (**c**). Comparison of (**c**) and (**d**), however, indicates that the substrate-to-intermediate conversion is about 18% over 30 min on ice in the crystallization buffer. This suggests that, while the background cyclization still occurs in the sample, a significant proportion of the substrate should be available to complex with Lsd19 upon mixing it with the substrate.




**Supplementary Figure 2.** Amino acid sequence alignment of the polyether epoxide hydrolases involved in the biosynthesis of lasalocid, monensin, nigericin, nanchangmycin and tetronomycin, along with structurally related $\Delta^5$-3-ketosteroid isomerases (KSIs), limonene-1,2-epoxide hydrolase (LEH). Numbering corresponds to Lsd19 residue numbering. Residues highlighted in yellow are proposed catalytic residues, and green are implicated in substrate recognition and discrimination. Residues with gray highlight are predicted to be located at the opening of the active site pocket as shown in **Supplementary Fig. 3a**.


a
1a
2a
3a
4a
+3 residues
+18 residues
+21 residues
V102
D38
E65
L36
Y14
M117
G104
F30
I97
D38
E65
F36
V112
Y14
F30
G99
I97
D38
E65
F36
A112
Y14
F30
G99
M97
D38
E65
F36
Y14
I112
T99
F30
Lsd19A (390 Å3)
MonBII (405 Å3)
NigBII (550 Å3)
NanIA (594 Å3)
1b
2b
3b
4b
Y251
E197
D170
F168
M266
H146
Y162
M253
A116
E64
D37
L35
L131
H13
Y29
L118
L132
E65
D38
F36
Y117
H14
L119
Y30
Y272
A193
E220
F191
M287
H169
Y185
L274
Lsd19B (240 Å3)
MonBI (330 Å3)
NigBI (360 Å3)
NanIB (160 Å3)


b
Group A
Group B
Lasalocid A
Monensin A
Nigericin
Nanchangmycin
R =
Cationomycin
Glabrescol
Ionophore Polyether
Squalene Polyether
ACP

**Supplementary Figure 3.** Comparison of polyether epoxide hydrolases and chemical structure of polyether natural products. **a,** Crystal structure of Lsd19 and homology models of the polyether epoxide hydrolases (PEHs) involved in the biosynthesis of monensin, nigericin and nanchangmycin. Homology model was built using the program suite MODELLER[1] and energy-minimized using Chimera[2]. Approximate volume of the binding pocket was calculated using the program 3V[3]. Red line is drawn with respect to the absolutely conserved Lsd19A E65 and the equivalent residues in other PEHs. Gray broken lines indicate C-terminal residues that were not modeled. The length of the non-modeled segment is as indicated in the figure. One PEH-B, the C-terminal domain of NanI (NanIB), carries an Ala residue in place of the catalytic Asp38, which may render this enzyme inactive. The homology model of NanIB shown here also carries an unusually small substrate binding pocket, suggesting that this protein may be inactive. Inspection of the structure of nanchangmycin reveals that, unlike majority of other APPA polyethers, its cyclic ethers are comprised of two 6,5-spiroketals. Our hypothesis of PEH-A-catalyzed 6,5-spiroketal formation suggests the possibility that NanIA may catalyze the formation of both cyclic ethers in nanchangmycin biosynthesis, while NanIB exists to maintain the activity of the NanIA domain. **b,** Comparison of the chemical structures of ionophore and squalene polyethers by aligning the cyclic ether ring structures. The nucleophilic alcohol that initiates the cyclization sequence proposed to be catalyzed by PEH-A occurs at 22 carbon atoms from the terminal carbon, while the corresponding reaction-initiating alcohol for PEH-B occurs at 10 carbon atoms from the terminal. These atom counts also hold well for other compounds, such as cationomycin and squalene-derived glabrescol.

1 Eswar, N. *et al.* Comparative protein structure modeling using MODELLER. *Curr. Protoc. Protein Sci.* **Chapter 2**, Unit 2.9 (2007).

2 Pettersen, E. F. *et al.* UCSF Chimera – A visualization system for exploratory research and analysis. *J. Comput. Chem.* **25**, 1605-1612. (2004).

3 Voss, N. R., Gerstein, M., Steitz, T. A. & Moore, P. B. The geometry of the ribosomal polypeptide exit tunnel. *J. Mol. Biol.* **360**, 893-906 (2006).

**Supplementary Data**

**Coordinates from the quantum chemical calculations and theozyme calculations**

**Brønsted acid catalyzed:**

**Substrate A:**

**Acid-A-5-1) 5-*exo*-tet, conformer 1 (not shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –425.426497 |
| G B2PLYP/6-31G(d): | –425.243659 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –425.611356 |
| E B2PLYP/6-31G(d) in CPCM water: | –425.504789 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –425.496813 |
| Imaginary harmonic frequency: | 211.85 |

| | | | |
|---|---|---|---|
| C | -1.544503 | 0.368102 | 0.443329 |
| H | -1.148715 | 0.496346 | 1.444022 |
| C | -0.943845 | -0.690350 | -0.347556 |
| H | -1.187036 | -0.694406 | -1.407686 |
| C | -2.339417 | 1.495778 | -0.156043 |
| H | -3.389064 | 1.221755 | -0.300806 |
| H | -2.323700 | 2.360693 | 0.506925 |
| H | -1.915638 | 1.778659 | -1.120954 |
| C | 0.231605 | -1.508313 | 0.081359 |
| H | 0.025386 | -2.554978 | -0.162749 |
| H | 0.357731 | -1.441056 | 1.164811 |
| C | 1.508455 | -1.066061 | -0.666522 |
| H | 2.303265 | -1.774976 | -0.419844 |
| H | 1.337712 | -1.145596 | -1.745065 |
| C | 1.980402 | 0.351418 | -0.346187 |
| H | 2.779879 | 0.597115 | -1.055368 |
| O | 0.846809 | 1.210101 | -0.603937 |
| H | 1.160760 | 2.128384 | -0.612370 |
| O | -2.251778 | -1.043162 | 0.481500 |
| H | -3.037945 | -1.043156 | -0.107247 |
| C | 2.500451 | 0.540931 | 1.073211 |
| H | 3.365446 | -0.101362 | 1.258721 |
| H | 2.818837 | 1.575641 | 1.228734 |
| H | 1.733944 | 0.312397 | 1.818831 |

**Acid-A-5-2) 5-*exo*-tet, conformer 2 (shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –425.427366 |
| G B2PLYP/6-31G(d): | –425.244162 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –425.612244 |
| E B2PLYP/6-31G(d) in CPCM water: | –425.505210 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –425.497269 |
| Imaginary harmonic frequency: | 228.32 |

| | | | |
|---|---|---|---|
| C | -1.757074 | 0.279580 | 0.534489 |
| H | -1.614502 | -0.020581 | 1.567722 |
| C | -0.997651 | -0.466358 | -0.461644 |
| H | -0.999207 | -0.059836 | -1.465154 |
| C | -2.290139 | 1.666679 | 0.283853 |
| H | -2.364813 | 2.216644 | 1.221937 |
| H | -1.624396 | 2.207297 | -0.390621 |
| H | -3.292799 | 1.641613 | -0.154349 |
| C | -0.034958 | -1.560472 | -0.110676 |
| H | 0.207557 | -2.130808 | -1.010724 |
| H | -0.528562 | -2.241985 | 0.589125 |
| C | 1.247854 | -1.005739 | 0.544798 |
| H | 1.000039 | -0.523513 | 1.497120 |
| H | 1.900664 | -1.851936 | 0.774240 |
| C | 1.989044 | -0.005359 | -0.329500 |
| H | 2.281692 | -0.493302 | -1.269861 |
| O | 1.014187 | 1.021326 | -0.616598 |
| H | 1.438275 | 1.701865 | -1.164195 |
| O | -2.528106 | -0.894257 | -0.112690 |
| H | -3.135328 | -0.551664 | -0.804500 |
| C | 3.217652 | 0.577216 | 0.351963 |
| H | 3.945607 | -0.206735 | 0.576028 |
| H | 3.710620 | 1.307957 | -0.295997 |
| H | 2.938137 | 1.075147 | 1.283839 |

**Acid-A-6-1) 6-*endo*-tet, conformer 1 (shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –425.427731 |
| G B2PLYP/6-31G(d): | –425.243877 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –425.612370 |
| E B2PLYP/6-31G(d) in CPCM water: | –425.505464 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –425.497560 |
| Imaginary harmonic frequency: | 278.66 |

| | | | |
|---|---|---|---|
| C | 1.403199 | 0.574628 | -0.334437 |
| H | 1.349067 | 0.527442 | -1.413720 |
| C | 1.097346 | -0.671677 | 0.364540 |
| H | 1.044338 | -0.602673 | 1.451477 |
| C | 1.947693 | 1.794159 | 0.308222 |
| H | 2.896890 | 2.082523 | -0.151269 |
| H | 1.246427 | 2.610601 | 0.110177 |
| H | 2.062097 | 1.690311 | 1.388522 |
| C | 0.120083 | -1.626957 | -0.262479 |
| H | 0.355785 | -2.643922 | 0.061895 |
| H | 0.258388 | -1.592579 | -1.345918 |
| C | -1.341870 | -1.273619 | 0.103660 |
| H | -1.986087 | -1.658488 | -0.691149 |
| H | -1.632209 | -1.790617 | 1.023097 |
| C | -1.625314 | 0.218668 | 0.309834 |
| H | -1.276143 | 0.524612 | 1.306136 |
| O | -0.845081 | 0.950988 | -0.676408 |
| H | -1.223352 | 1.842673 | -0.764203 |
| O | 2.498652 | -0.893744 | -0.082587 |
| H | 3.112529 | -0.740017 | 0.663894 |
| C | -3.101839 | 0.550765 | 0.176045 |
| H | -3.687488 | -0.021475 | 0.899892 |
| H | -3.288451 | 1.611867 | 0.369185 |
| H | -3.456136 | 0.305988 | -0.828363 |

**Acid-A-6-2) 6-*endo*-tet, conformer 2 (not shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –425.422704 |
| G B2PLYP/6-31G(d): | –425.238909 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –425.607283 |
| E B2PLYP/6-31G(d) in CPCM water: | –425.500939 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –425.492944 |
| Imaginary harmonic frequency: | 282.78 |

| | | | |
|---|---|---|---|
| C | -1.281657 | 0.502263 | 0.333493 |
| H | -0.851240 | 0.629663 | 1.318701 |
| C | -1.036824 | -0.778832 | -0.313005 |
| H | -1.352394 | -0.840806 | -1.354298 |
| C | -2.190574 | 1.549910 | -0.192695 |
| H | -2.963292 | 1.794639 | 0.540676 |
| H | -1.600333 | 2.457817 | -0.345153 |
| H | -2.641763 | 1.273594 | -1.147071 |
| C | 0.197536 | -1.574471 | 0.012192 |
| H | 0.017779 | -2.616278 | -0.268151 |
| H | 0.365919 | -1.557378 | 1.092629 |
| C | 1.414745 | -1.032824 | -0.760120 |
| H | 2.248525 | -1.726700 | -0.623131 |
| H | 1.190727 | -1.022874 | -1.832042 |
| C | 1.881448 | 0.362409 | -0.345630 |
| H | 2.647491 | 0.681090 | -1.061169 |
| O | 0.737328 | 1.250684 | -0.511778 |
| H | 1.040779 | 2.160791 | -0.353075 |
| O | -2.171037 | -1.068306 | 0.616354 |
| H | -3.016391 | -1.064878 | 0.122360 |
| C | 2.445649 | 0.457631 | 1.065244 |
| H | 3.323388 | -0.185607 | 1.168035 |
| H | 2.763408 | 1.480985 | 1.285896 |
| H | 1.715124 | 0.160397 | 1.822307 |

**Substrate B:**

**Acid-B-5-1) 5-exo-tet, conformer 1 (shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –464.703436 |
| G B2PLYP/6-31G(d): | –464.493670 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –464.904987 |
| E B2PLYP/6-31G(d) in CPCM water: | –464.776883 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –464.769440 |
| Imaginary harmonic frequency: | 123.17 |

| | | | |
|---|---|---|---|
| C | 1.442221 | 0.639015 | -0.517942 |
| H | 0.873390 | 1.131643 | -1.302286 |
| C | 0.766432 | -0.546314 | 0.036052 |
| C | 2.241181 | 1.607526 | 0.309925 |
| H | 2.872162 | 1.116823 | 1.053827 |
| H | 2.873811 | 2.211294 | -0.344320 |
| H | 1.555038 | 2.276679 | 0.833628 |
| C | -0.329142 | -1.191468 | -0.747442 |
| H | -0.037044 | -2.227669 | -0.945667 |
| H | -0.451713 | -0.690195 | -1.709041 |
| C | -1.667925 | -1.213853 | 0.035132 |
| H | -2.403499 | -1.740361 | -0.578106 |
| H | -1.543973 | -1.793901 | 0.953656 |
| C | -2.174877 | 0.182687 | 0.380576 |
| H | -2.977531 | 0.079368 | 1.120480 |
| O | -1.044498 | 0.827122 | 1.009286 |
| H | -1.303206 | 1.724294 | 1.277381 |
| O | 2.215287 | -0.440520 | -1.178939 |
| H | 3.042218 | -0.591300 | -0.677853 |
| C | -2.686130 | 0.989040 | -0.805184 |
| H | -3.547519 | 0.495339 | -1.262396 |
| H | -3.012583 | 1.982035 | -0.481969 |
| H | -1.916769 | 1.120738 | -1.570758 |
| C | 1.203532 | -1.172854 | 1.312130 |
| H | 1.131805 | -2.261023 | 1.270781 |
| H | 2.204288 | -0.877747 | 1.626591 |
| H | 0.503066 | -0.8115 | 2.073792 |

**Acid-B-6-1) 6-*endo*-tet, conformer 1 (shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –464.697908 |
| G B2PLYP/6-31G(d): | –464.486800 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –464.898740 |
| E B2PLYP/6-31G(d) in CPCM water: | –464.772366 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –464.764808 |
| Imaginary harmonic frequency: | 288.92 |

| | | | |
|---|---|---|---|
| C | 1.186443 | 0.805057 | -0.461856 |
| H | 0.975153 | 0.935037 | -1.513494 |
| C | 1.065932 | -0.582281 | 0.018930 |
| C | 1.772508 | 1.957521 | 0.266178 |
| H | 2.725353 | 2.239950 | -0.193018 |
| H | 1.108197 | 2.814361 | 0.124764 |
| H | 1.908656 | 1.784078 | 1.332480 |
| C | 0.039554 | -1.413744 | -0.722592 |
| H | 0.332115 | -2.465870 | -0.661086 |
| H | 0.081321 | -1.135666 | -1.778543 |
| C | -1.404111 | -1.241941 | -0.192369 |
| H | -2.078558 | -1.529897 | -1.003327 |
| H | -1.589767 | -1.944337 | 0.625668 |
| C | -1.791708 | 0.156179 | 0.311220 |
| H | -1.487079 | 0.272558 | 1.358832 |
| O | -1.050563 | 1.133305 | -0.471769 |
| H | -1.433104 | 2.011280 | -0.300242 |
| O | 2.372406 | -0.622855 | -0.709767 |
| H | 3.099456 | -0.574957 | -0.056110 |
| C | -3.285381 | 0.414563 | 0.198071 |
| H | -3.843355 | -0.338186 | 0.760998 |
| H | -3.551193 | 1.394160 | 0.607609 |
| H | -3.599677 | 0.370792 | -0.847509 |
| C | 1.240181 | -0.910992 | 1.485080 |
| H | 1.472397 | -1.973985 | 1.586049 |
| H | 2.042704 | -0.3353 | 1.953082 |
| H | 0.322117 | -0.713791 | 2.040155 |

**Acid-B-6-2) 6-*endo*-tet, conformer 2 (not shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –464.691549 |
| G B2PLYP/6-31G(d): | –464.480693 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –464.892724 |
| E B2PLYP/6-31G(d) in CPCM water: | –464.766476 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –464.758847 |
| Imaginary harmonic frequency: | 305.51 |

| | | | |
|---|---|---|---|
| C | 0.939750 | 0.826949 | -0.424571 |
| H | 0.336013 | 1.079660 | -1.286594 |
| C | 0.987111 | -0.600387 | -0.094331 |
| C | 1.762682 | 1.913314 | 0.166264 |
| H | 2.469033 | 2.292375 | -0.578769 |
| H | 1.096020 | 2.746435 | 0.402560 |
| H | 2.291529 | 1.619581 | 1.071091 |
| C | -0.203151 | -1.421559 | -0.555447 |
| H | 0.102955 | -2.471145 | -0.593356 |
| H | -0.455190 | -1.131304 | -1.579568 |
| C | -1.421785 | -1.276204 | 0.373218 |
| H | -2.200612 | -1.960280 | 0.024233 |
| H | -1.158032 | -1.601666 | 1.383574 |
| C | -2.023897 | 0.127145 | 0.449736 |
| H | -2.756389 | 0.132582 | 1.264259 |
| O | -0.939760 | 1.023336 | 0.841229 |
| H | -1.322116 | 1.899146 | 1.022504 |
| O | 1.965667 | -0.480340 | -1.230708 |
| H | 2.873772 | -0.445425 | -0.865657 |
| C | 1.627280 | -1.046371 | 1.198596 |
| H | 0.958721 | -0.819095 | 2.031072 |
| H | 2.578330 | -0.544019 | 1.391654 |
| H | 1.803557 | -2.123733 | 1.175378 |
| C | -2.697728 | 0.608304 | -0.828071 |
| H | -3.543707 | -0.038138 | -1.075326 |
| H | -3.087937 | 1.622589 | -0.701893 |
| H | -2.014778 | 0.611325 | -1.681694 |

**Brønsted base catalyzed:**

**Substrate A:**

**Base-A-5-1) 5-*exo*-tet, conformer 1 (shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –500.838023 |
| G B2PLYP/6-31G(d): | –500.660838 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –501.089957 |
| E B2PLYP/6-31G(d) in CPCM water: | –500.920468 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –500.911935 |
| Imaginary harmonic frequency: | 413.38 |

| | | | |
|---|---|---|---|
| C | -1.808657 | -0.531039 | 0.559781 |
| H | -1.511388 | -1.348430 | 1.249610 |
| C | -0.839940 | -0.270453 | -0.497658 |
| H | -1.006477 | 0.625571 | -1.074013 |
| C | -2.294819 | 0.661275 | 1.371782 |
| H | -3.183770 | 0.394484 | 1.956614 |
| H | -1.507480 | 1.014147 | 2.046306 |
| H | -2.572606 | 1.473241 | 0.691397 |
| C | -0.010957 | -1.397813 | -1.068267 |
| H | 0.247295 | -1.175377 | -2.111125 |
| H | -0.621864 | -2.303564 | -1.068892 |
| C | 1.273893 | -1.575311 | -0.251412 |
| H | 1.024089 | -1.990334 | 0.734175 |
| H | 1.972761 | -2.271687 | -0.738756 |
| C | 1.856749 | -0.168357 | -0.053590 |
| H | 2.320449 | 0.130939 | -1.024813 |
| O | 0.809517 | 0.654730 | 0.310452 |
| H | 0.620222 | 2.094002 | -0.535833 |
| O | -2.592616 | -0.919029 | -0.518788 |
| C | 2.972133 | -0.145037 | 1.000868 |
| H | 3.809321 | -0.808977 | 0.742797 |
| H | 3.358255 | 0.873266 | 1.111246 |
| H | 2.560439 | -0.454784 | 1.967591 |
| O | 0.298473 | 2.915709 | -1.014099 |
| H | -0.522648 | 3.096639 | -0.535838 |

**Base-A-6-1) 6-*endo*-tet, conformer 1 (shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –500.832029 |
| G B2PLYP/6-31G(d): | –500.653939 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –501.084317 |
| E B2PLYP/6-31G(d) in CPCM water: | –500.914136 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –500.905671 |
| Imaginary harmonic frequency: | 462.70 |

| | | | |
|---|---|---|---|
| C | 0.528889 | -1.071565 | 0.336045 |
| H | 0.303865 | -0.738998 | 1.337862 |
| C | 1.701932 | -0.483235 | -0.273034 |
| H | 1.794315 | -0.704203 | -1.357066 |
| C | -0.062857 | -2.370436 | -0.118885 |
| H | 0.299284 | -3.199868 | 0.494867 |
| H | -1.150769 | -2.314784 | -0.042610 |
| H | 0.209654 | -2.567441 | -1.159774 |
| C | 1.856292 | 1.019379 | -0.055268 |
| H | 2.849632 | 1.347439 | -0.396621 |
| H | 1.822197 | 1.209929 | 1.024615 |
| C | 0.747822 | 1.787225 | -0.791235 |
| H | 0.914087 | 2.872712 | -0.708498 |
| H | 0.808293 | 1.541246 | -1.860246 |
| C | -0.696717 | 1.449148 | -0.329102 |
| H | -1.355372 | 2.046510 | -1.002958 |
| O | -0.990783 | 0.103459 | -0.449119 |
| H | -2.492964 | -0.490119 | -0.032121 |
| O | 2.360756 | -1.366199 | 0.573137 |
| O | -3.366298 | -0.988008 | 0.013340 |
| H | -3.469197 | -1.235986 | -0.916134 |
| C | -0.974825 | 1.986517 | 1.091909 |
| H | -0.811556 | 3.070919 | 1.169623 |
| H | -2.015661 | 1.773282 | 1.354758 |
| H | -0.338423 | 1.493141 | 1.832868 |

**Base-A-6-2) 6-*endo*-tet, conformer 2 (not shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –500.828129 |
| G B2PLYP/6-31G(d): | –500.649943 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –501.080490 |
| E B2PLYP/6-31G(d) in CPCM water: | –500.910443 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –500.901953 |
| Imaginary harmonic frequency: | 452.47 |

| | | | |
|---|---|---|---|
| C | 1.029027 | 0.941377 | -0.302100 |
| H | 1.056623 | 0.940682 | -1.380084 |
| C | 1.770882 | -0.133189 | 0.334338 |
| H | 1.608544 | -0.210915 | 1.428670 |
| C | 0.714446 | 2.229124 | 0.399148 |
| H | 1.405456 | 3.020480 | 0.093306 |
| H | -0.308343 | 2.535032 | 0.170113 |
| H | 0.803759 | 2.104560 | 1.482375 |
| C | 1.554693 | -1.492394 | -0.322730 |
| H | 2.328873 | -2.200782 | 0.004296 |
| H | 1.706771 | -1.345843 | -1.398110 |
| C | 0.135119 | -2.050242 | -0.050801 |
| H | -0.219492 | -2.587795 | -0.941403 |
| H | 0.165852 | -2.790365 | 0.762968 |
| C | -0.917873 | -0.969018 | 0.320430 |
| H | -0.728050 | -0.703208 | 1.385579 |
| O | -0.865004 | 0.142132 | -0.506296 |
| H | -2.069372 | 1.230131 | -0.158651 |
| O | 2.869299 | 0.632833 | -0.035189 |
| C | -2.326264 | -1.583908 | 0.275745 |
| H | -2.427149 | -2.456407 | 0.936487 |
| H | -3.064040 | -0.830642 | 0.566538 |
| H | -2.551089 | -1.897238 | -0.750558 |
| O | -2.807458 | 1.915920 | -0.095612 |
| H | -3.043216 | 2.014725 | -1.028932 |

**Substrate B:**

**Base-B-5-1) 5-*exo*-tet, conformer 1 (not shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –540.101772 |
| G B2PLYP/6-31G(d): | –539.897825 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –540.368070 |
| E B2PLYP/6-31G(d) in CPCM water: | –540.183046 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –540.174637 |
| Imaginary harmonic frequency: | 415.47 |

| | | | |
|---|---|---|---|
| C | 1.523832 | 0.197990 | -0.818832 |
| H | 0.945865 | 0.249460 | -1.766087 |
| C | 0.838446 | -0.595561 | 0.203819 |
| C | 2.016341 | 1.601188 | -0.486384 |
| H | 2.592493 | 1.596016 | 0.444141 |
| H | 2.683885 | 1.949768 | -1.283786 |
| H | 1.174880 | 2.295254 | -0.393054 |
| C | 0.081596 | -1.826555 | -0.253322 |
| H | 0.635875 | -2.724844 | 0.041615 |
| H | 0.053206 | -1.824852 | -1.347000 |
| C | -1.339606 | -1.864108 | 0.326142 |
| H | -1.953160 | -2.624604 | -0.179291 |
| H | -1.292334 | -2.144460 | 1.385991 |
| C | -1.920635 | -0.440238 | 0.231549 |
| H | -2.803684 | -0.389660 | 0.909668 |
| O | -0.919096 | 0.418360 | 0.636715 |
| H | -1.125630 | 2.070192 | 0.320004 |
| O | 2.453195 | -0.832959 | -0.751076 |
| O | -1.164795 | 3.072089 | 0.286402 |
| H | -0.691494 | 3.299763 | 1.098837 |
| C | 1.295345 | -0.523679 | 1.642902 |
| H | 2.326549 | -0.872934 | 1.725847 |
| H | 1.228106 | 0.500015 | 2.015958 |
| H | 0.653712 | -1.140790 | 2.276881 |
| C | -2.441959 | -0.119428 | -1.182139 |
| H | -3.267215 | -0.781149 | -1.482256 |
| H | -2.799696 | 0.914547 | -1.209179 |
| H | -1.63596 | -0.209295 | -1.917026 |

**Base-B-5-2) 5-*exo*-tet, conformer 2 (shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –540.101767 |
| G B2PLYP/6-31G(d): | –539.897975 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –540.368531 |
| E B2PLYP/6-31G(d) in CPCM water: | –540.181755 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –540.173489 |
| Imaginary harmonic frequency: | 411.49 |

| | | | |
|---|---|---|---|
| C | 1.783600 | 0.203497 | -0.816607 |
| H | 1.485246 | -0.416835 | -1.688427 |
| C | 1.097151 | -0.202225 | 0.411104 |
| C | 1.757978 | 1.661861 | -1.255559 |
| H | 2.453798 | 1.809032 | -2.090403 |
| H | 0.748024 | 1.942494 | -1.571348 |
| H | 2.074658 | 2.319356 | -0.441817 |
| C | 0.722244 | -1.668409 | 0.538738 |
| H | 0.572728 | -1.916464 | 1.598093 |
| H | 1.563914 | -2.263965 | 0.178622 |
| C | -0.562210 | -1.972661 | -0.240099 |
| H | -0.358834 | -1.913812 | -1.317030 |
| H | -0.928712 | -2.988240 | -0.027697 |
| C | -1.572694 | -0.877822 | 0.127383 |
| H | -1.954174 | -1.119357 | 1.151086 |
| O | -0.896976 | 0.326517 | 0.085156 |
| H | -1.966310 | 1.585945 | 0.483430 |
| O | 2.907682 | -0.243559 | -0.136120 |
| C | -2.792032 | -0.866973 | -0.805773 |
| H | -3.355447 | -1.810096 | -0.772841 |
| H | -3.453872 | -0.045558 | -0.518437 |
| H | -2.457486 | -0.693400 | -1.835176 |
| O | -2.667300 | 2.302930 | 0.492567 |
| H | -2.657987 | 2.564226 | -0.438660 |
| C | 1.202827 | 0.619497 | 1.671649 |
| H | 1.316523 | 1.682011 | 1.450365 |
| H | 0.287995 | 0.497641 | 2.25363 |
| H | 2.061494 | 0.299332 | 2.268771 |

**Base-B-6-1) 6-*endo*-tet, conformer 1 (shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –540.098425 |
| G B2PLYP/6-31G(d): | –539.893102 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –540.366883 |
| E B2PLYP/6-31G(d) in CPCM water: | –540.179598 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –540.171215 |
| Imaginary harmonic frequency: | 450.71 |

| | | | |
|---|---|---|---|
| C | 0.779545 | 0.992135 | -0.514256 |
| H | 0.632698 | 0.966671 | -1.580671 |
| C | 1.665451 | -0.057566 | -0.010221 |
| C | 0.502825 | 2.294745 | 0.178227 |
| H | 1.203146 | 3.066078 | -0.155032 |
| H | -0.517934 | 2.609613 | -0.046044 |
| H | 0.590842 | 2.201765 | 1.263323 |
| C | 1.352630 | -1.400720 | -0.681683 |
| H | 2.175906 | -2.108732 | -0.504581 |
| H | 1.345592 | -1.203636 | -1.758773 |
| C | -0.003100 | -2.016982 | -0.250545 |
| H | -0.426163 | -2.561171 | -1.106812 |
| H | 0.153592 | -2.768457 | 0.537850 |
| C | -1.069655 | -1.002091 | 0.258144 |
| H | -0.840929 | -0.811232 | 1.330491 |
| O | -1.104335 | 0.169210 | -0.476959 |
| H | -2.309621 | 1.213627 | 0.007064 |
| O | 2.639236 | 0.740522 | -0.609892 |
| C | -2.457691 | -1.664667 | 0.238931 |
| H | -2.492344 | -2.590050 | 0.830999 |
| H | -3.200682 | -0.963763 | 0.630469 |
| H | -2.730181 | -1.903017 | -0.795843 |
| O | -3.074483 | 1.859310 | 0.121823 |
| H | -3.429559 | 1.875199 | -0.778120 |
| C | 1.916767 | -0.214295 | 1.490978 |
| H | 2.862972 | -0.756936 | 1.605563 |
| H | 2.045299 | 0.763219 | 1.961465 |
| H | 1.133393 | -0.764861 | 2.021431 |

**Base-B-6-2) 6-*endo*-tet, conformer 2 (not shown):**

| | |
|---|---|
| E B2PLYP/6-31G(d): | –540.120931 |
| G B2PLYP/6-31G(d): | –539.916602 |
| E B2PLYP/6-311++G(d,p)//B2PLYP/6-31G(d): | –540.386573 |
| E B2PLYP/6-31G(d) in CPCM water: | –540.173868 |
| E B2PLYP/6-31G(d) in CPCM dichloromethane: | –540.165500 |
| Imaginary harmonic frequency: | 460.18 |

| | | | |
|---|---|---|---|
| C | -0.443203 | -0.888839 | -0.563764 |
| H | 0.007798 | -0.528470 | -1.475331 |
| C | -1.595793 | -0.127968 | -0.110327 |
| C | -0.133190 | -2.305013 | -0.178688 |
| H | -0.605904 | -3.005040 | -0.872636 |
| H | 0.949445 | -2.444167 | -0.205044 |
| H | -0.483002 | -2.527959 | 0.831541 |
| C | -1.403324 | 1.382698 | -0.311654 |
| H | -2.358534 | 1.901071 | -0.135105 |
| H | -1.164035 | 1.534436 | -1.371029 |
| C | -0.299977 | 1.970940 | 0.582456 |
| H | -0.218782 | 3.056060 | 0.411300 |
| H | -0.589626 | 1.847771 | 1.633389 |
| C | 1.099045 | 1.320188 | 0.404681 |
| H | 1.732017 | 1.786073 | 1.195559 |
| O | 1.073157 | -0.055569 | 0.573447 |
| H | 2.486312 | -0.865088 | 0.231654 |
| O | -2.221565 | -0.812134 | -1.153608 |
| O | 3.294218 | -1.463770 | 0.162838 |
| H | 3.332548 | -1.816624 | 1.062971 |
| C | -2.155531 | -0.452360 | 1.275666 |
| H | -2.404179 | -1.514687 | 1.328100 |
| H | -1.441894 | -0.213366 | 2.070134 |
| H | -3.080552 | 0.113106 | 1.443790 |
| C | 1.749793 | 1.738123 | -0.932271 |
| H | 1.857702 | 2.828603 | -1.017489 |
| H | 2.743172 | 1.284491 | -1.001697 |
| H | 1.164119 | 1.388963 | -1.788123 |

**Theozyme Calculations:**

**Reactant complex:**

E M06-2X/6-311++G(d,p): –1040.112246
E B2PLYP/6-311++G(d,p): –1039.527359
E MP2/6-311++G(d,p): –1037.608561
E M06-2X/6-311++G(d,p) in CPCM ether: –1040.175689

| | | | |
|---|---|---|---|
| C | 3.395290 | 3.763822 | -1.227179 |
| C | 2.918229 | 2.680774 | -0.305882 |
| O | 2.010275 | 2.936236 | 0.501778 |
| O | 3.468111 | 1.519209 | -0.368338 |
| C | -4.591892 | 2.204480 | 1.802885 |
| C | -4.222577 | 1.056158 | 0.841926 |
| C | -3.898785 | -0.222556 | 1.321209 |
| C | -4.142527 | 1.265304 | -0.507718 |
| C | -3.515591 | -1.242871 | 0.443603 |
| C | -3.748788 | 0.247989 | -1.376120 |
| C | -3.441204 | -0.982062 | -0.890074 |
| O | -3.055005 | -1.981449 | -1.738440 |
| H | 4.488245 | 3.771115 | -1.282607 |
| H | 3.025913 | 3.574854 | -2.242240 |
| H | -3.691633 | 2.738311 | 2.124825 |
| H | -5.254536 | 2.922870 | 1.312122 |
| H | -3.940712 | -0.419768 | 2.390321 |
| H | -4.373780 | 2.247604 | -0.915561 |
| H | -3.251386 | -2.229189 | 0.812132 |
| H | -3.666452 | 0.424732 | -2.444069 |
| H | -2.122197 | -2.164968 | -1.497837 |
| H | 2.852778 | 0.555288 | 0.802275 |
| C | 0.052012 | -0.910999 | 0.432416 |
| H | 0.317788 | -1.465829 | 1.330799 |
| C | 0.820820 | -1.251301 | -0.762062 |
| C | -0.510631 | 0.467169 | 0.664546 |
| H | -1.131441 | 0.779509 | -0.180161 |
| H | -1.135904 | 0.486989 | 1.561662 |
| H | 0.315734 | 1.180530 | 0.787457 |
| C | 1.895472 | -2.314234 | -0.670533 |
| H | 1.900265 | -2.867465 | -1.621392 |
| H | 1.605793 | -3.033201 | 0.105663 |
| C | 3.303031 | -1.758506 | -0.407294 |
| H | 4.040189 | -2.545649 | -0.623041 |
| H | 3.509646 | -0.930469 | -1.095454 |
| C | 3.553006 | -1.237908 | 1.020345 |
| H | 4.587211 | -0.847585 | 1.022001 |
| O | 2.655775 | -0.234036 | 1.399099 |

```
O  -0.523804   -1.759932   -0.589815
C   1.005528   -0.225946   -1.854097
H   0.082794    0.337271   -2.008923
H   1.807026    0.467190   -1.568919
H   1.275906   -0.716235   -2.797866
C   3.471115   -2.342904    2.069068
H   4.151009   -3.171626    1.838752
H   3.728120   -1.933706    3.050390
H   2.450936   -2.736327    2.133345
H   3.026052    4.734929   -0.893831
H  -5.095221    1.822153    2.695640
```

**6-*endo*-tet, TS:**

E M06-2X/6-311++G(d,p): –1040.073011
E B2PLYP/6-311++G(d,p): –1039.498711
E MP2/6-311++G(d,p): –1037.574385
E M06-2X/6-311++G(d,p) in CPCM ether: –1040.188353

| | | | |
|---|---|---|---|
| C | 3.516764 | 3.682785 | -1.343758 |
| C | 2.982583 | 2.739291 | -0.307519 |
| O | 2.025044 | 3.099751 | 0.396153 |
| O | 3.535827 | 1.586178 | -0.166866 |
| C | -4.646146 | 2.499805 | 1.372004 |
| C | -4.216023 | 1.228577 | 0.612082 |
| C | -3.922800 | 0.035453 | 1.290420 |
| C | -4.050469 | 1.241799 | -0.745884 |
| C | -3.484174 | -1.096963 | 0.595194 |
| C | -3.601913 | 0.113775 | -1.431786 |
| C | -3.325314 | -1.030369 | -0.754824 |
| O | -2.885558 | -2.137837 | -1.424004 |
| H | 4.604158 | 3.776352 | -1.257146 |
| H | 3.311549 | 3.286713 | -2.344577 |
| H | -3.771310 | 3.075801 | 1.691863 |
| H | -5.258634 | 3.143687 | 0.734146 |
| H | -4.033191 | -0.004838 | 2.372449 |
| H | -4.258477 | 2.153589 | -1.303586 |
| H | -3.228950 | -2.014704 | 1.113914 |
| H | -3.452472 | 0.132420 | -2.506859 |
| H | -1.943140 | -2.257894 | -1.068930 |
| H | 2.765343 | 0.705137 | 0.598822 |
| C | 0.573207 | -0.855569 | 0.757393 |
| H | 0.709649 | -1.562392 | 1.564588 |
| C | 0.611708 | -1.469884 | -0.577297 |
| C | -0.160691 | 0.422898 | 1.032525 |
| H | -1.137707 | 0.384498 | 0.543093 |
| H | -0.312712 | 0.557557 | 2.106015 |
| H | 0.410003 | 1.281751 | 0.660299 |
| C | 1.773889 | -2.453951 | -0.746911 |
| H | 1.691552 | -2.934892 | -1.731216 |
| H | 1.632524 | -3.245689 | -0.000644 |
| C | 3.147159 | -1.792313 | -0.585623 |
| H | 3.944065 | -2.524570 | -0.777398 |
| H | 3.269576 | -0.989127 | -1.322280 |
| C | 3.381201 | -1.168417 | 0.799279 |
| H | 4.349772 | -0.649054 | 0.760406 |
| O | 2.404985 | -0.185783 | 1.105060 |
| O | -0.586352 | -2.060386 | -0.197384 |
| C | 0.508072 | -0.489131 | -1.741755 |

| | | | |
|---|---|---|---|
| H | -0.394688 | 0.118823 | -1.635336 |
| H | 1.377297 | 0.177856 | -1.784498 |
| H | 0.433827 | -1.043199 | -2.684827 |
| C | 3.438666 | -2.195913 | 1.926037 |
| H | 4.255936 | -2.906829 | 1.759706 |
| H | 3.603383 | -1.685368 | 2.878978 |
| H | 2.508971 | -2.767724 | 2.003899 |
| H | 3.044182 | 4.659027 | -1.236423 |
| H | -5.226395 | 2.246460 | 2.264399 |

**6-*endo*-tet, product complex:**

E M06-2X/6-311++G(d,p): –1040.121747
E B2PLYP/6-311++G(d,p): –1039.537843
E MP2/6-311++G(d,p): –1037.620533
E M06-2X/6-311++G(d,p) in CPCM ether: –1040.188353

| | | | |
|---|---|---|---|
| C | -3.531112 | 3.871715 | 1.310628 |
| C | -2.965869 | 2.998011 | 0.230611 |
| O | -1.958510 | 3.381260 | -0.386079 |
| O | -3.544148 | 1.880009 | -0.036272 |
| C | 4.737316 | 2.632354 | -1.035611 |
| C | 4.225770 | 1.319033 | -0.409513 |
| C | 3.937082 | 0.196082 | -1.200276 |
| C | 3.981732 | 1.227162 | 0.933498 |
| C | 3.424981 | -0.973403 | -0.627444 |
| C | 3.460391 | 0.063161 | 1.496872 |
| C | 3.189674 | -1.011707 | 0.712489 |
| O | 2.678710 | -2.154163 | 1.261422 |
| H | -4.622327 | 3.818845 | 1.355139 |
| H | -3.142646 | 3.531516 | 2.275996 |
| H | 3.910157 | 3.273869 | -1.363534 |
| H | 5.331510 | 3.202247 | -0.313305 |
| H | 4.119940 | 0.241415 | -2.274284 |
| H | 4.192357 | 2.084910 | 1.574157 |
| H | 3.188615 | -1.844560 | -1.229176 |
| H | 3.258699 | -0.011168 | 2.561246 |
| H | 1.478242 | -2.340923 | 0.414306 |
| H | -2.935475 | 1.283606 | -0.550760 |
| C | -1.031070 | -0.937767 | -1.035657 |
| H | -1.155620 | -1.731792 | -1.787052 |
| C | -0.417414 | -1.622302 | 0.209597 |
| C | -0.173107 | 0.170589 | -1.611560 |
| H | 0.864716 | -0.171823 | -1.658394 |
| H | -0.516732 | 0.444641 | -2.614067 |
| H | -0.224810 | 1.064036 | -0.981277 |
| C | -1.470937 | -2.596075 | 0.777296 |
| H | -1.084187 | -3.025460 | 1.709005 |
| H | -1.552865 | -3.423692 | 0.061302 |
| C | -2.834151 | -1.941085 | 1.000900 |
| H | -3.582804 | -2.676240 | 1.325396 |
| H | -2.759857 | -1.186217 | 1.792536 |
| C | -3.323585 | -1.249822 | -0.272347 |
| H | -4.167579 | -0.594089 | -0.025772 |
| O | -2.326340 | -0.356167 | -0.765173 |

| | | | |
|---|---|---|---|
| O | 0.668797 | -2.361472 | -0.259303 |
| C | -0.012890 | -0.586025 | 1.261704 |
| H | 0.761477 | 0.076767 | 0.867174 |
| H | -0.869289 | 0.025680 | 1.571236 |
| H | 0.419566 | -1.095239 | 2.128453 |
| C | -3.781962 | -2.224511 | -1.356553 |
| H | -4.677353 | -2.759133 | -1.022224 |
| H | -4.024258 | -1.674725 | -2.270943 |
| H | -3.015306 | -2.966759 | -1.593309 |
| H | -3.198057 | 4.892114 | 1.133725 |
| H | 5.366705 | 2.433983 | -1.910135 |

**5-*exo*-tet, TS:**

E M06-2X/6-311++G(d,p): –1040.068007
E B2PLYP/6-311++G(d,p): –1039.494759
E MP2/6-311++G(d,p): –1037.567966
E M06-2X/6-311++G(d,p) in CPCM ether: –1040.129835

| | | | |
|---|---|---|---|
| C | 3.357042 | 3.851214 | -1.285948 |
| C | 2.851169 | 2.837685 | -0.303248 |
| O | 1.905737 | 3.143319 | 0.441790 |
| O | 3.414278 | 1.682001 | -0.249911 |
| C | -4.739590 | 2.427423 | 1.511063 |
| C | -4.316883 | 1.212246 | 0.660654 |
| C | -4.001729 | -0.020410 | 1.253029 |
| C | -4.179639 | 1.315809 | -0.696570 |
| C | -3.570206 | -1.101307 | 0.476112 |
| C | -3.738043 | 0.238760 | -1.464093 |
| C | -3.440014 | -0.945085 | -0.869589 |
| O | -3.006266 | -2.002494 | -1.618808 |
| H | 4.447714 | 3.817493 | -1.365898 |
| H | 2.953058 | 3.627667 | -2.280132 |
| H | -3.861903 | 2.984390 | 1.855706 |
| H | -5.363825 | 3.109747 | 0.926665 |
| H | -4.085329 | -0.132570 | 2.332534 |
| H | -4.403284 | 2.260427 | -1.189782 |
| H | -3.305425 | -2.051229 | 0.929020 |
| H | -3.609280 | 0.330906 | -2.538084 |
| H | 3.025437 | 4.846479 | -0.989675 |
| H | -5.305403 | 2.112629 | 2.393083 |
| C | 4.515460 | -1.197670 | 1.667284 |
| C | 3.640401 | -1.128470 | 0.423645 |
| C | 3.117284 | -2.482114 | -0.041264 |
| C | 1.980854 | -2.186494 | -1.021288 |
| C | 1.029020 | -1.179182 | -0.404761 |
| C | 0.691483 | 0.091010 | -1.143987 |
| O | 2.493153 | -0.346556 | 0.674301 |
| C | 0.088643 | -1.701206 | 0.604587 |
| H | 4.213328 | -0.664599 | -0.395434 |
| H | 2.731240 | -3.037712 | 0.822833 |
| H | 3.904787 | -3.089248 | -0.503127 |
| H | 1.402986 | -3.080488 | -1.258329 |
| H | 2.393629 | -1.781991 | -1.953386 |
| H | 0.493693 | 0.909907 | -0.445954 |
| O | -0.639800 | -2.185287 | -0.465990 |
| H | 1.538663 | 0.391199 | -1.766174 |
| H | 4.842380 | -0.191231 | 1.943175 |

| | | | |
|---|---|---|---|
| H | 3.938875 | -1.616221 | 2.499026 |
| H | 5.399966 | -1.823349 | 1.497552 |
| H | -0.189168 | -0.078285 | -1.766657 |
| H | 2.776542 | 0.679358 | 0.355730 |
| H | -2.118392 | -2.228610 | -1.208347 |
| C | -0.548518 | -0.675676 | 1.527036 |
| H | -1.085548 | 0.082884 | 0.951508 |
| H | -1.269379 | -1.157362 | 2.196128 |
| H | 0.229587 | -0.190068 | 2.125823 |
| H | 0.547830 | -2.497185 | 1.225165 |

**5-*exo*-tet, product complex:**

E M06-2X/6-311++G(d,p): –1040.111511
E B2PLYP/6-311++G(d,p): –1039.530511
E MP2/6-311++G(d,p): –1037.611594
E M06-2X/6-311++G(d,p) in CPCM ether: –1040.179610

| | | | |
|---|---|---|---|
| C | 3.614347 | 3.866542 | -1.132708 |
| C | 2.996204 | 3.020908 | -0.059575 |
| O | 1.971951 | 3.429455 | 0.511667 |
| O | 3.546688 | 1.899529 | 0.248751 |
| C | -4.754001 | 2.788388 | 0.920155 |
| C | -4.238959 | 1.456734 | 0.337118 |
| C | -3.997154 | 0.344299 | 1.157914 |
| C | -3.946063 | 1.336946 | -0.993856 |
| C | -3.481427 | -0.842620 | 0.625588 |
| C | -3.421400 | 0.155550 | -1.516477 |
| C | -3.196835 | -0.908753 | -0.703654 |
| O | -2.682038 | -2.067877 | -1.212506 |
| H | 4.705083 | 3.790054 | -1.144604 |
| H | 3.246564 | 3.517269 | -2.102932 |
| H | -3.944463 | 3.371568 | 1.376077 |
| H | -5.204442 | 3.404351 | 0.134774 |
| H | -4.217140 | 0.412432 | 2.223827 |
| H | -4.118942 | 2.185681 | -1.657363 |
| H | -3.285863 | -1.710960 | 1.247471 |
| H | -3.185270 | 0.058685 | -2.571982 |
| H | 3.298098 | 4.896350 | -0.982036 |
| H | -5.512059 | 2.619503 | 1.693190 |
| C | 4.158090 | -1.208122 | 1.362598 |
| C | 3.368543 | -1.162185 | 0.065367 |
| C | 2.999120 | -2.533531 | -0.501758 |
| C | 1.690774 | -2.237915 | -1.231332 |
| C | 1.014778 | -1.197233 | -0.331327 |
| C | 0.156637 | -0.222574 | -1.115294 |
| O | 2.132012 | -0.483146 | 0.292064 |
| C | 0.219331 | -1.916903 | 0.792167 |
| H | 3.937079 | -0.593183 | -0.687748 |
| H | 2.837886 | -3.248216 | 0.313204 |
| H | 3.786045 | -2.931752 | -1.149715 |
| H | 1.035239 | -3.102900 | -1.349294 |
| H | 1.896645 | -1.805653 | -2.218269 |
| H | -0.231306 | 0.578018 | -0.478691 |
| O | -0.705530 | -2.830793 | 0.290368 |
| H | 0.744018 | 0.231427 | -1.921855 |
| H | 4.388156 | -0.200037 | 1.722103 |

| | | | |
|---|---|---|---|
| H | 3.571515 | -1.726398 | 2.128030 |
| H | 5.104034 | -1.741454 | 1.217606 |
| H | -0.696103 | -0.767109 | -1.541599 |
| H | 2.867036 | 1.302585 | 0.645530 |
| H | -1.477598 | -2.441206 | -0.278901 |
| C | -0.362269 | -0.923746 | 1.798029 |
| H | -1.142331 | -0.307473 | 1.345145 |
| H | -0.819209 | -1.477392 | 2.624567 |
| H | 0.423089 | -0.271385 | 2.194925 |
| H | 0.971283 | -2.514854 | 1.338047 |